NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 402

# TOXICOLOGY AND CARCINOGENESIS

# STUDIES OF FURAN

## (CAS NO. 110-00-9)

# IN F344/N RATS AND B6C3F$_1$ MICE

## (GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

## FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements, and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

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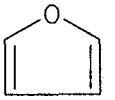
# ABSTRACT



**FURAN**

CAS No. 110-00-9

$C_4H_4O$ Molecular Weight: 68.08

**Synonyms:** Divinylene oxide, tetrole, furfuran, oxole, 1,4-epoxy-1,3-butadiene, axole, oxacyclopentadiene


Furan serves as an intermediate in the synthesis and preparation of numerous linear polymers used to prepare temperature-resistant structural laminates and to prepare copolymers used in machine dishwashing products as alternatives to phosphorus- and nitrogen-containing detergents. Toxicology and carcinogenesis studies were conducted by administering furan (purity > 99%) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, *Drosophila melanogaster*, mouse bone marrow cells, mouse L5178Y lymphoma cells, and Chinese hamster ovary cells.

## *16-Day Studies*

Groups of five male rats received doses of 0, 5, 10, 20, 40, or 80 mg of furan per kg of body weight and groups of five female rats and five mice of each sex received doses of 0, 10, 20, 40, 80, and 160 mg/kg in corn oil by gavage. All male and female mice and female rats that received 160 mg/kg, all male and female rats and all male and four female mice that received 80 mg/kg, and three male mice that received 40 mg/kg died by day 8. Final mean body weights of male rats that received 20 mg/kg and of male and female rats that received 40 mg/kg were significantly lower than controls. Final mean body weights of male mice that received 10 or 20 mg/kg were significantly greater than controls. Mottled and enlarged livers were observed at necropsy in male rats that received 20, 40, or 80 mg/kg and in females that received 40, 80, or 160 mg/kg. No lesions were observed at necropsy that were considered related to furan administration in mice.

## *13-Week Studies*

Groups of 10 rats of each sex and groups of 10 female mice received doses of 0, 4, 8, 15, 30, or 60 mg of furan per kg of body weight, and groups of 10 male mice received doses of 0, 2, 4, 8, 15, or 30 mg/kg in corn oil by gavage. Nine male and four female rats that received 60 mg/kg died before the end of the studies. There were no chemical-related deaths in mice. Final mean body weights of male rats that received 15 or 30 mg/kg and female rats that received 60 mg/kg were significantly lower than controls. Final mean body weights of male mice that received 60 mg/kg were significantly lower than controls. Relative and absolute liver weights in both sexes of rats and mice were increased in groups that received furan, as were relative and absolute kidney weights in female rats that received furan. Thymus weights were decreased in all groups of rats that received furan.

Toxic lesions of the liver (bile duct hyperplasia, cholangiofibrosis, cytomegaly and degeneration of hepatocytes, and nodular hyperplasia of hepatocytes) were associated with furan administration in all dose groups of rats; the severity of the lesions increased with dose. Kidney lesions (tubule dilatation and necrosis of tubule epithelium) were present in rats that received 30 or 60 mg/kg. Thymic atrophy and testicular or ovarian atrophy were also observed in rats exposed to 60 mg/kg furan. Toxic liver lesions (cytomegaly, degeneration, and necrosis of hepato-

cytes) were also present in all groups of furan-exposed mice. Bile duct hyperplasia and cholangiofibrosis were observed in groups of mice receiving 30 or 60 mg/kg.

Doses selected for the 2-year studies of rats and mice were based on the hepatotoxicity associated with exposure to furan.

### *2-Year Studies*

Groups of 70 rats of each sex were administered 2, 4, or 8 mg furan per kg body weight in corn oil by gavage 5 days per week for 2 years. After 9 and 15 months of chemical exposure, 10 rats per group were evaluated for the presence of treatment-associated lesions. Groups of 50 mice of each sex received doses of 8 or 15 mg/kg furan 5 days per week for 2 years.

*Body Weight and Survival.* Mean body weights of male rats that received 8 mg/kg furan were lower than controls from approximately week 73 to the end of the study. Survival of male and female rats that received 8 mg/kg was lower than controls from approximately week 85 to the end of the studies as a result of moribund condition associated with liver and biliary tract neoplasms and mononuclear cell leukemia.

Mean body weights of male and female mice that received 15 mg/kg furan were lower than controls during the studies. Survival of low- and high-dose male and high-dose female mice was lower than controls from approximately week 80 to the end of the studies as a result of moribund condition associated with liver neoplasms.

*Neoplastic and Nonneoplastic Lesions.* Cholangiocarcinoma of the liver occurred in all groups of dosed rats (males: control, 0/50; low dose, 43/50; mid dose, 48/50; high dose, 49/50; females: 0/50; 49/50; 50/50; 48/50) and was present in many rats of each sex at the 9- and 15-month interim evaluations (9-month: males - 0/10, 5/10, 7/10, 10/10; females - 0/10, 4/10, 9/10, 10/10; 15-month: males - 0/10, 7/10, 9/10, 6/10; females - 0/10, 9/10, 9/10, 7/10). Hepatocellular adenomas or carcinomas (combined) were significantly increased in male rats after 2 years of chemical administration (1/50, 5/50, 22/50, 35/50) and hepatocellular adenomas were significantly increased in female rats (0/50, 2/50, 4/50, 7/50); hepatocellular neoplasms were not observed at the 9- or 15-month interim evaluations. Increased incidences of numerous nonneoplastic liver lesions were present in rats administered furan. These lesions included biliary tract fibrosis, hyperplasia, chronic inflammation, and proliferation and hepatocyte cytomegaly, cytoplasmic vacuolization, degeneration, nodular hyperplasia, and necrosis.

The incidence of mononuclear cell leukemia was increased in male and female rats that received 4 or 8 mg/kg furan (males: 8/50, 11/50, 17/50, 25/50; females: 8/50, 9/50, 17/50, 21/50); the incidence in the 8 mg/kg groups of each sex exceeded the historical control ranges for corn oil gavage studies.

The severity of nephropathy increased with dose and the incidence was significantly increased in all groups of dosed rats; this increased severity was accompanied by an associated increased incidence of parathyroid hyperplasia (renal secondary hyperparathyroidism).

The incidence of forestomach hyperplasia was increased in male and female rats (males: 1/50, 4/49, 7/50, 6/50; females: 0/50, 2/50, 5/50, 5/50) and the incidence of subacute inflammation of the forestomach was increased in female rats (0/50, 1/50, 5/50, 6/50). No forestomach neoplasms were observed in males; a squamous papilloma was present in one low-dose female.

The incidences of hepatocellular adenomas and carcinomas were significantly increased in mice receiving furan (males: adenoma - 20/50, 33/50, 42/50; carcinoma - 7/50, 32/50, 34/50; females: adenoma - 5/50, 31/50, 48/50; carcinoma - 2/50, 7/50, 27/50). The incidences of numerous nonneoplastic hepatocellular lesions were increased in dosed mice. These lesions included hepatocyte cytomegaly, degeneration, necrosis, multifocal hyperplasia, and cytoplasmic vacuolization and biliary tract dilatation, fibrosis, hyperplasia, and inflammation.

The incidences of benign pheochromocytoma and focal hyperplasia of the adrenal medulla were increased in low- and high-dose male and in high-dose female mice (benign pheochromocytoma: males - 1/49, 6/50, 10/50; females - 2/50, 1/50, 6/50).

The incidences of squamous papilloma, focal inflammation, and papillary hyperplasia of the forestomach were increased in male mice (squamous papilloma:

0/49, 1/50, 3/50; focal inflammation: 9/49, 13/50, 21/50; papillary hyperplasia: 7/49, 14/50, 22/50).

### *Stop-Exposure Study*

A separate 2-year study was conducted in which 50 male rats were administered 30 mg/kg furan in corn oil by gavage 5 days per week for 13 weeks and then maintained for the remainder of the 2 years without additional furan administration. Groups of 10 animals were evaluated for the presence of treatment-related lesions at the end of the 13-week period of furan administration and at 9 and 15 months.

*Neoplastic and Nonneoplastic Lesions.* Cholangiocarcinoma of the liver occurred with an overall incidence of 100% (40/40) and hepatocellular carcinoma occurred with an overall incidence of 15% (6/40) in stop-exposure male rats that survived at least 9 months. Cholangiocarcinoma was observed in all 10 males at both the 9-month and 15-month interim evaluations. Hepatocellular carcinoma was first observed in 2 males at the 15-month interim evaluation.

### *Genetic Toxicology*

Furan was negative for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 in the presence and the absence of exogenous metabolic activation (S9). Furan was negative for the induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* when administered either by feeding or by injection. *In vitro* tests for genotoxicity in mammalian cells, however, were positive. Furan induced trifluorothymidine resistance in mouse L5178Y lymphoma cells in the absence of S9, and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, with and without S9. Furan administered to male $B6C3F_1$ mice by intraperitoneal injection induced chromosomal aberrations but not sister chromatid exchanges in bone marrow cells.

### *Conclusions*

Under the conditions of these 2-year gavage studies there was *clear evidence of carcinogenic activity** of furan in male and female F344/N rats based on increased incidences of cholangiocarcinoma and hepatocellular neoplasms of the liver and on increased incidences of mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of furan in male and female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms of the liver and benign pheochromocytomas of the adrenal gland.

Nonneoplastic liver lesions associated with furan administration in rats and mice included biliary tract fibrosis, hyperplasia, inflammation, and proliferation, as well as hepatocellular cytomegaly, degeneration, hyperplasia, necrosis, and vacuolization. In rats, increased severity of nephropathy with an associated increased incidence of parathyroid hyperplasia was associated with exposure to furan.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of peer review comments and the public discussion on this Technical Report appears on page 11.

## Summary of the 2-Year Carcinogenesis and the Genetic Toxicology Studies of Furan

| Male F344/N Rats | Female F344/N Rats | Male $B6C3F_1$ Mice | Female $B6C3F_1$ Mice |
|---|---|---|---|
| **Doses** | | | |
| 0, 2, 4, or 8 mg/kg of furan in corn oil by gavage 5 days per week | 0, 2, 4, or 8 mg/kg of furan in corn oil by gavage 5 days per week | 0, 8, or 15 mg/kg of furan in corn oil by gavage 5 days per week | 0, 8, or 15 mg/kg of furan in corn oil by gavage 5 days per week |
| **Body weights** | | | |
| High-dose less than control | Dosed similar to control | Dosed less than control | High-dose less than control |
| **2-Year survival rates** | | | |
| 33/50; 28/50; 26/50; 16/50 | 34/50; 32/50; 28/50; 19/50 | 33/50; 17/50; 16/50 | 29/50; 25/50; 2/50 |
| **Nonneoplastic effects** | | | |
| Kidney: nephropathy<br>Liver: biliary tract - dilatation, chronic inflammation, fibrosis, and hyperplasia; hepatocyte - cytomegaly, degeneration, and necrosis<br>Parathyroid: hyperplasia | Kidney: nephropathy<br>Liver: biliary tract - chronic focal inflammation, cyst, focal fibrosis, focal hyperplasia, and metaplasia; hepatocyte - cytomegaly, cytoplasmic vacuolization, focal degeneration, focal hyperplasia, and focal necrosis<br>Parathyroid: hyperplasia | Liver: biliary tract - chronic focal inflammation, cyst, focal fibrosis, focal hyperplasia, and metaplasia; hepatocyte - cytomegaly, cytoplasmic vacuolization, focal degeneration, focal hyperplasia, and focal necrosis | Liver: biliary tract - dilatation, chronic inflammation, fibrosis, and hyperplasia; hepatocyte - cytomegaly, degeneration, and necrosis |
| **Neoplastic effects** | | | |
| Liver: cholangiocarcinoma - 0/50; 43/50; 48/50; 49/50 hepatocellular adenoma or carcinoma - 1/50; 5/50; 22/50; 35/50<br>Mononuclear cell leukemia: 8/50; 11/50; 17/50; 25/50 | Liver: cholangiocarcinoma - 0/50; 49/50; 50/50; 48/50 hepatocellular adenoma or carcinoma - 0/50; 2/50; 4/50; 8/50<br>Mononuclear cell leukemia: 8/50; 9/50; 17/50; 21/50 | Liver: hepatocellular adenoma or carcinoma - 26/50; 44/50; 50/50<br>Adrenal gland: benign pheochromocytoma - 1/49; 6/50; 10/50 | Liver: hepatocellular adenoma or carcinoma - 7/50; 34/50; 50/50<br>Adrenal gland: benign pheochromocytoma - 2/50; 1/50; 6/50 |
| **Level of evidence of carcinogenic activity** | | | |
| Clear evidence | Clear evidence | Clear evidence | Clear evidence |
| **Genetic toxicology** | | | |
| Gene Mutations | | | |
| *Salmonella typhimurium in vitro*: | Negative with and without S9 in strains TA98, TA100, TA1535, TA1537 | | |
| L5178Y/TK$^{+/-}$ mouse lymphoma *in vitro*: | Positive without S9 | | |
| Sister Chromatid Exchanges | | | |
| Chinese hamster ovary cells *in vitro*: | Positive with and without S9 | | |
| $B6C3F_1$ mouse bone marrow cells *in vivo*: | Negative when administered by injection | | |
| Chromosomal Aberrations | | | |
| Chinese hamster ovary cells *in vitro*: | Positive with and without S9 | | |
| $B6C3F_1$ mouse bone marrow cells *in vivo*: | Positive when administered by injection | | |
| Sex-linked Recessive Lethal Mutations | | | |
| *Drosophila melanogaster*: | Negative when administered in feed or by injection | | |

# EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the technical report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that because of major flaws cannot be evaluated (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence of carcinogenic activity** describes studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study of carcinogenic activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement is selected for a particular experiment, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

# PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the NTP draft Technical Report on furan on 11 March 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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# SUMMARY OF PEER REVIEW COMMENTS

On March 11, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of furan received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of furan by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and reviewing the neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions were *clear evidence of carcinogenic activity* for furan for male and female F344/N rats and for male and female B6C3F$_1$ mice.

Dr. Goodman, a principal reviewer, agreed with the proposed conclusions. He commented on the four widely used *in vitro* tests for genetic toxicity and noted the inability of three of the assays, mutagenesis in mouse lymphoma cells and chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells, to improve on the ability of mutagenesis in *Salmonella typhimurium* for predicting carcinogenicity of chemicals in long-term rodent studies. He thought presentation of data from these assays should be very limited in the report. Further, he said the possibility should be considered that sister chromatid exchanges and chromosomal aberrations might be artifacts resulting from lysosome breakdown secondary to cytotoxicity and not from direct chemical action on DNA.

Mr. Beliczky, the second principal reviewer, agreed with the proposed conclusions. He said the discussion and comparison of furan and furan compounds was excellent, and the presence of uncommon mutations in cellular genes suggested they were chemical related.

Dr. Hayden, the third principal reviewer, agreed with the proposed conclusions. He suggested more illustration of differentiation between cholangiofibrosis and cholangiocellular carcinoma. Dr. Irwin said photomicrographs would be added. Dr. Hayden commented on the frequent discrepancies in furan dose formulations between the study laboratory and the analytical chemistry laboratory and asked whether the animals had received the proper doses. Dr. Irwin responded that this was an analytical problem due to the high volatility of furan. Considerable care was taken with the dosing solutions in the animal rooms to minimize potential loss.

Dr. Davis commented on the variable incidence of mononuclear cell leukemia with time. Dr. J.K. Haseman, NIEHS, said the NTP database is updated at least yearly with data from older studies being dropped and from newer studies added so as to maintain about a 5-year window. Dr. Hayden and Dr. Zeise thought increased incidences of urinary bladder papillomas in female rats and squamous cell papillomas of the forestomach in male mice deserved more discussion. Mr. Beliczky said that, based on the carcinogenicity of furan and the wide industrial use, there should be information included on potential worker exposure. Dr. J.C. Haartz, NIOSH, said the most recent exposure data indicated only 14 plants with 35 workers potentially exposed.

Dr. Goodman moved that the Technical Report on furan be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity.* Mr. Beliczky seconded the motion, which was accepted unanimously with 10 votes.